XI THE HEMATOPOIETIC SYSTEM

THE CASTLE APPROACH

Pernicious anemia was usually fatal until 1926, when Minot and Murphy first described the beneficial effects of feeding liver to those patients, suggesting that the disease was caused by a nutritional or metabolic defect. In early 1927, at age 30, W.B. Castle conceived the theory that the relation of the gastric abnormality achlorhydria to the hematologic abnormality anemia was causal. For the next 2 years, Castle directed meticulous clinical experiments to demonstrate that the gastric abnormality caused the hematologic abnormality.

He first found that oral administration of gastric juice (intrinsic factor) or beef muscle (extrinsic factor, vitamin B_{12}) alone was ineffectual in treatment of pernicious anemia. Administration of a mixture of both, however, rendered the patient "erythropoietically active as judged by prompt reticulocyte responses and gains in red cell counts" (Castle, 1982). Castle presented preliminary data to the American Society for Clinical Investigation in 1928, concluding that "the achylia gastrica of the pernicious anemia patient is operative in the production of a deficiency causing the disease through a failure of the patient's stomach to produce the substance apparently found during digestion in the normal stomach" (Kass, 1978). That substance he later identified as intrinsic factor, which is secreted by parietal cells of the stomach and binds to vitamin B_{12} in the distal ilium. Others before him had appreciated that achlorhydria and anemia were associated, but no causal relationship had been demonstrated.

The son of a biologist, Castle was born in Cambridge, Massachusetts, in 1897. He attended Harvard College and graduated from Harvard Medical School in 1921. After an internship at the Massachusetts General Hospital, he spent 2 years in the physiologic laboratory of Walter B. Cannon. In 1925, at age 28, Castle returned to clinical medicine as a resident under Francis Peabody, the

first director of the newly opened Thorndike Memorial Laboratory of Boston City Hospital. There Castle eventually conducted the research on pernicious anemia that distinguished him as a great physician–scientist:

> *I found myself fascinated with this mysterious and fatal disease but made no scientific progress over the next two years, my continued presence perhaps being tolerated because I was taking care of some of the patients on the Thorndike Ward and occasionally able to persuade a pernicious anemia patient to permit trephine biopsy of the tibial marrow for Dr. Peabody's research. (Castle, 1982)*

In 1937, at age 40, he became professor of medicine of Harvard University, and in 1948, following the retirement of Minot, Castle became the third director of the Thorndike. He became the George Roberts Minot Professor of Medicine in 1957, and on retiring from his hospital administrative positions in 1963, he was appointed Francis Weld Peabody Faculty Professor of Medicine. He was honored with an appointment in 1968, at age 71, as Faculty Professor Emeritus and Distinguished Physician in the Veterans Hospital.

What also distinguishes the clinical investigation of Castle was his direct responsibility for data. He cared for the patients, carried out the assays, and monitored all procedures. Eugene Stead, who was chief resident at the Thorndike from 1937 to 1939 and later chairman of the Department of Medicine at Emory University and then Duke University, had these recollections:

> *William Castle was the most original thinker of my Thorndike mentors. I first met him on the steps of Burnham Building. A resident was describing the course of a patient with kidney disease and his projected treatment. I pointed out to him the error of his ways, and the resident defended himself by telling me that he was following Castle's instruction. I replied that I didn't believe Castle knew much about this problem. I sensed without turning around that a third person had come near enough to hear this exchange. On turning around, the newcomer said, "I'm Bill Castle, and I'd like to take part in this discussion." I was, of course, very embarrassed; but not Castle. He was too secure in his good sense to be annoyed by criticism. We agreed that I knew more about this particular problem than he did. Castle was always willing to look at any critical problem, and he never felt uneasy if he did not have much specific knowledge about the problem. He could identify the problem and the points at issue. He then extracted from his colleagues what they knew and added any information that he had. Knowing the general state of knowledge and the techniques available to investigators, Castle could make a reasonable guess about the knowledge that could be obtained from the library, and various members agreed to look up the relevant paper. Knowing the state of the art, he could project the next experimental approach to unearth new knowledge. A wise man, he had defined a clinical problem, collated information from persons present at the bedside, decided on the necessary library work and projected the next clinical research on the problem—all without a complete and comprehensive knowledge of the subject. He taught me that I need not know everything to be an effective teacher. When I visit other hospitals, the resident is frequently surprised that I will see any type of patient in front of a large group without special preparation. The Castle approach gives me that freedom. (Stead, 1983)*

—CHARLES STEWART ROBERTS

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145 An Overview of the Hematopoietic System

CHARLES M. HUGULEY, JR.

The approach to the patient with a hematologic illness is the same as for any illness. The physician who is thorough and thoughtful in history taking and physical examination will seldom be far off in his assessments. The major emphasis in hematologic diagnosis is on laboratory studies and, as often as not, these may be not only necessary but sufficient to establish the diagnosis. Nevertheless, there are many instances in which an abnormal laboratory finding sends the physician back to the patient for pursuit, in greater depth, of the history or physical examination to clarify the diagnosis. The information in the following chapters tends to be arranged with this in mind; that is, given the suspicion of a particular disease, which are the appropriate questions and what are the pertinent physical findings to support or reject the suggested diagnosis? The collection of the subjective and objective database is not a set mode but a kinetic and highly interactive process requiring alertness and thoughtfulness to correlate and probe continually. I plan, therefore, to point out here some areas in which specialized approaches to additional history or physical examination will illuminate abnormalities found in the initial database. The clues to the need for these specialized procedures may well be found during the initial history and examination by the thoughtful physician. The procedures themselves are well described in the following chapters.

Hematological diseases involve the red blood cells, the granulocytes, the lymphocytes and monocytes of the immune system, and the platelets and the clotting proteins of the hemostatic system.

History

Anemia (Chapter 147) may produce pallor, exertional dyspnea, and fatigability. The duration of such symptoms may pinpoint the time of onset. Their absence in a severe anemia suggests a long-standing problem with time for physiologic adaptation. A symptom of jaundice suggests a hemolytic anemia. Such anemias are often hereditary; the family history should be explored, not only for a similar anemia, but also for splenectomies, cholecystectomies early in life, or painful crises. In general practice, 30 to 40% of anemias are secondary: the anemia of chronic inflammatory disease and the anemia of renal failure. Therefore, the history of concomitant disease is always important. The next most common cause of anemia (25 to 35%) is iron deficiency. The content of iron in the diet should be assessed. A careful questioning should be made for a possible source of bleeding, especially through the menstrual history and the history of gastrointestinal blood loss.

Polycythemia often produces plethora and the time of first recognition of a red face may help. A long duration, especially if associated with cyanosis, would be more in keeping with a secondary polycythemia, whereas a duration of only a few years or months would suggest polycythemia vera.

Granulocytopenia and *immune system diseases* are characterized by susceptibility to infection. The frequency and type of infection should be carefully documented. The various white cells, granulocytes, monocytes, and lymphocytes are often involved in a malignant proliferation. This may produce a lymphoma or leukemia. These may result from the administration of drugs in the distant past, especially chemotherapeutic drugs for other illnesses. The patient may have been aware of a large lymph node for a long time. These diseases produce cytopenias leading to symptoms attributable to anemia, thrombocytopenia, or granulocytopenia.

Diseases of the platelets or clotting system lead to bleeding or thrombosis (Chapter 146). Hereditary bleeding problems are usually manifest early in life and lead to the appellation "bleeder." The family history should be explored for bleeders, joint-bleeding, bleeding after surgery or after dental extractions. Special attention should be paid to the mode of heredity, especially sex linkage. The age of the patient at onset and the frequency and type of bleeding is important. Hemophiliacs will suffer hemarthroses and hematuria, apparently spontaneously, but very seldom bleed elsewhere without injury. Petechial bleeding is the rule with thrombocytopenia, but is seldom seen with coagulation disorders except for coumadin overdosage. In preoperative screening for possible bleeding problems, the mainstay is questioning for a family history or a past history of bleeding with surgery or with dental extractions. A drug history is important in a patient who has a bleeding problem or who is screened preoperatively for the possibility. Aspirin and other nonsteroidal anti-inflammatory drugs interfere with platelet function and may lead to oozing after injury. A number of common drugs may produce thrombocytopenia (e.g., quinine in tonic water). Patients may forget to mention chronic coumadin therapy. A new drug given to a patient on coumadin may interact with coumadin, leading to an augmentation or diminution of its effect and a change in the status of anticoagulation.

A history of exposure to drugs or chemicals is often important with any hematologic disease. Anemia, granulocytopenia, thrombocytopenia, or any combination of these may be produced by drugs. Some drugs, such as the cancer chemotherapy drugs, regularly produce cytopenia as an expected and dose-related side effect that is a considered risk and is reversible. Others produce cytopenia by idiosyncratic mechanisms in a rare patient, constituting an unexpected hazard unrelated to the pharmacologic therapeutic effect. The mechanisms for some of these are immunologic, some are metabolic, and others are unknown. With most cytopenia, the process readily reverses on discontinuation of the drug, but with aplastic anemia it very seldom does. A long list of drugs and chemicals have been implicated in cytopenia. Benzene is the most active chemical, but there are

many others. Among drugs, the most frequently involved are chloramphenicol, phenylbutazone, sulfonamides of all sorts including nonantibacterial ones, gold salts, and antiepileptics.

Physical Examination

The hallmark physical finding in *anemia* is pallor. Conversely, in *polycythemia* it is plethora or rubor. However, the variation between individuals in complexion is such that casual inspection will often fail to elicit these findings except in extreme variations of the red cell count. Comparison of the patient's palm with that of the observer is very helpful. In addition, if the fingers are hyperextended to drive blood from the palms, the depths of the palmar lines will remain red. If they are not red, the hemoglobin concentration will be less than about 8 g/dl. For polycythemia, plethora is best observed in the conjunctiva or the underside of the tip of the tongue. The presence of jaundice is a helpful finding in anemia as pointed out under history.

It is always necessary to check for the presence of splenomegaly in a hematologic illness. The technique is well described in Chapter 150. Measurement of the spleen is important in comparing changes in size as an index of progression of disease or response to therapy. In measuring the spleen, I find it ridiculous to attempt to guess consistently the position of the mid-clavicular line 45 cm from the clavicle. I trace in ink the tip of the spleen during quiet breathing and draw a line along the costal margin. The perpendicular distance of the tip from the costal margin is easily reproducible from day to day. For a large spleen, I trace the outline and measure the distance of the tip above or below the umbilicus and of the right border of the spleen to the left or right of the umbilicus. Similar considerations apply to lymph nodes. I grasp a node lightly between forefinger and thumb and measure the distance apart of the two digits. This is easier than trying to use calipers, and I believe it is just as accurate.

The patient with severe *granulocytopenia* is unable to make pus. Since many manifestations of infection—pus, inflammation, etc.—are due to granulocytes, the patient with agranulocytosis may have less indications of the locus of infection than usual. Draining abscesses may look like punched-out ulcers with little redness or swelling, exuding a thin serous material rather than pus.

A careful search for lymph nodes in all the lymph-node-bearing areas of the body must be made in the patient with leukemia or lymphoma as well as palpation for splenomegaly or hepatomegaly (Chapters 149 and 150). Other masses in the abdomen or elsewhere should be examined for, as well as mediastinal widening or pleural effusion.

Sometimes one forgets a careful examination of the skin. Petechiae on the lower extremities are easily missed. Skin involvement in a lymphoproliferative disease may be of very great significance and may be manifested only as a scaly dermatitis.

The type of bleeding in a bleeding disorder is often of importance: for example, apparently spontaneous ecchymoses versus bleeding only at the site of venipuncture or after surgery. Some distinguish dangerous "wet purpura" with GI tract bleeding or other active blood loss from less ominous "dry purpura" with only petechiae and a few small ecchymoses. The former demands more immediate action than the latter.